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Supernumerary Ring Chromosome 17 Identified by Fluorescent In Situ Hybridization

Kerry Fagan[1]* and Matthew Edwards[2]
[1]*Cytogenetics Unit, Hunter Area Pathology Service, Newcastle, New South Wales, Australia*
[2]*Hunter Genetics, Western Suburbs Hospital, Newcastle, New South Wales, Australia*

We present a patient with multiple anomalies and severe developmental delay. A small supernumerary ring chromosome was found in 40% of her lymphocyte cells at birth. The origin of the marker chromosome could not be determined by GTG banding, but fluorescent in situ hybridization (FISH) later identified the marker as deriving from chromosome 17. Am. J. Med. Genet. 69:352–355, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: supernumerary marker chromosomes; fluorescence in situ hybridization; ring marker chromosome 17

INTRODUCTION

In situ hybridization has become a valuable tool for identification of chromosome abnormalities. While identification based on size and shape of a marker chromosome can be obtained through standard cytogenetic procedures in some cases, DNA probes offer the most specific means of characterization. We report on a child born with multiple anomalies who was found to be mosaic for a marker (ring) chromosome derived from chromosome 17. The duplicated segment apparently included bands 17p13→q21.3. To our knowledge, this is the first report of a supernumerary marker chromosome containing chromosome 17 euchromatin. Identification of the chromosomal origin of the marker was not possible by routine banding techniques, but became possible with the advent of fluorescent in situ hybridization (FISH). We compare the clinical findings of our patient with those in other patients reported with duplication of various segments of chromosome 17.

CLINICAL REPORT

The patient was born to a 27-year-old mother and 30-year-old father by cesarean section because of fetal bradycardia during labor at 41 weeks after an otherwise uncomplicated gestation. The patient had 2 healthy sibs and no relevant family history. At birth she weighed 3,400 g (30th centile), was 45 cm long (2nd centile), had a head circumference (OFC) of 36.5 cm (75th centile), and was noted to have a large anterior fontanelle (Fig. 1), left iris coloboma, indistinct superior orbital ridges, downslanting palpebral fissures, hypertelorism, dystopia canthorum, small cupped ears

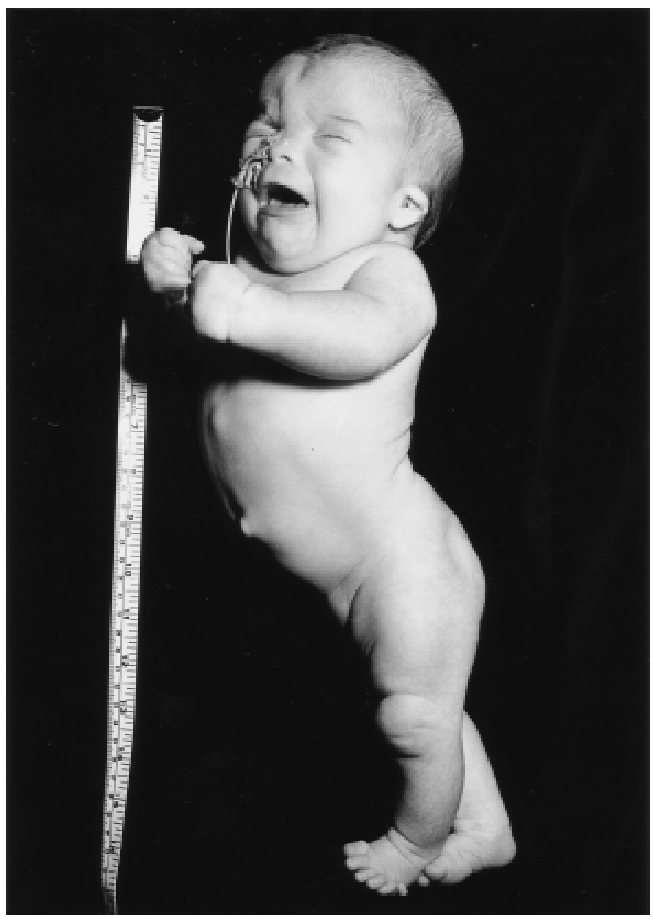

Fig. 1. The proband as a newborn.

*Correspondence to: Kerry Fagan, Cytogenetics Unit, Hunter Area Pathology Service, Locked Bag no. 1, Newcastle Mail Exchange, New South Wales 2310, Australia.

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with hypoplastic lobules lacking a superior crus of the antehelix, anteverted nostrils, and smooth philtrum. The infant had short fingers and toes, single transverse palmar creases, cutaneous syndactyly of the fourth and fifth fingers, short thumbs, a single flexion crease on the left fifth finger, short middle fingers equal in length to the ring fingers, bilateral equinovalgus and metatarsus valgus deformities, and postaxial polydactyly of each foot and the right hand. Other anomalies included pectus excavatum, hirsutism of the forehead and back, and a sacral dimple. Tube feeding was required primarily because of inability to swallow, which had probably contributed to severe pneumonia at age 3 months; tube feeds were continued until age 18 months.

At age $5\frac{4}{12}$ years, the patient weighed 12.45 kg (1st centile), and was 92 cm long (1st centile), with an OFC of 50.4 cm (60th centile). In the blind left eye she had microphthalmia, dislocated lens, and cataract, and in the right eye there was a marked reduction of vision, with convergent strabismus (Fig. 2), perception of large colored objects at 2 m distance, and a tendency to regard smaller objects held in the hands at a distance of 20 cm. The forehead was broad with a left cowlick, synophrys, low anterior hairline especially at the temples, and malar hypoplasia. The dentition was crowded and still deciduous, and the nose was small with a broad bridge. Inner intercanthal distance (4 cm), interpupillary distance (6 cm), and outer canthal distance (9 cm) were all >97th centile. There was scoliosis of the thoracic spine convex to the right, which could be corrected passively. Peripheral muscle bulk was markedly reduced in the upper and lower limbs, with hypotonia and absent deep tendon reflexes. The hip adductors and Achilles tendons were tight, with ankle dorsiflexion limited to 20° and talonavicular subluxation on passive movement past that point. Finger dermatoglyphics (1–5) were A, U, W, U, and U (left), and U, U, U, W, and U (right) (A, arch; U, ulnar loop; W, whorl). The skin over the dorsum of the hands and feet was soft and doughy. The feet were tiny, measuring 10.5 cm in length, and the toes were very small. Bilateral equinovalgus and metatarsus valgus deformity of the foot was present. The patient could sit and roll around on the floor, but could not crawl or walk, and the overall level of function was equivalent to age 8–9 months. Bilateral severe sensorineural hearing loss was treated with hearing aids, which enabled behavioral responses to 60-dB sounds. Expressive language was limited to squealing, and some interest was displayed in sport programs on TV upon insertion of middle-ear ventilation tubes and the use of hearing aids. Chronic constipation has been difficult to manage; in the past few months the patient has started to chew, having previously been fed on purees. There were no seizures.

CYTOGENETIC RESULTS

GTG-banded chromosome analyses were performed at birth and at age 5 years. At birth, the karyotype was 46,XX/47,XX,+mar. The C-band-positive ring-shaped marker chromosome was evident in 40% of lymphocytes. The parents had normal chromosomes.

Fig. 2. The proband aged five years.

A repeat lymphocyte culture at age 5 years failed to show the marker in 60 cells. Fluorescent in situ hybridization (FISH) studies were performed with painting probes (CAMBIO, Cambridge, UK) on the original preparations; a signal with the chromosome 17-specific probe was shown on the two normal chromosomes 17 and on the marker. Once the chromosomal origin of the marker had been established, the lack of GTG band pattern indicated the karyotype was probably 46,XX/47,XX, +r(17)(?p13q21.3) (Fig. 3).

DISCUSSION

The chromosomal origins of supernumerary marker chromosomes may now be identified using fluorescent in situ hybridization (FISH). Recent studies have shown they can originate from chromosomes 1–4, 6–9, 11, 12, 14–16, 17cen, 18–20, and 13/21 X and Y [Blennow et al., 1993, 1995; Callen et al., 1992; Crolla et al., 1992; Daniel et al., 1994; Gravholt and Friedrich, 1995; Leanacox et al., 1994; Plattner et al., 1993a,b; Rauch et al., 1992; Melnyk and Dewald, 1994; Michalski et al., 1993; Wiktor et al., 1993]. The evidence of reports so far indicates that the risk of phenotypic abnormalities is low if the marker originates from chromosomes 14,

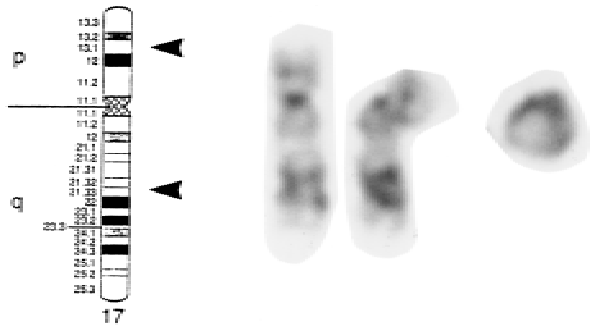

Fig. 3. GTG-bands and ideogram of chromosome 17 and marker.

15, 13/21, 1, 9, or 16, and if the size is small and the heterochromatic content of the marker is high [Blennow et al., 1993; Michalski et al., 1993]. If the marker is bisatellited and identified as an inv dup(15), the risk of abnormality is greater if genes in the Prader-Willi/Angelman syndrome region (PWS/AS) are in 3 or 4 copies [Leana-Cox et al., 1994]. If the marker is identified as an i(18p) or is a ring derived from an autosome, the carrier has a high risk of phenotypic abnormality [Callen et al., 1992].

Duplications of long-arm and short-arm segments of chromosome 17 were described in the early cytogenetic literature, but not confirmed using FISH [Palutke et al., 1976; Yamamoto et al., 1979]. Trisomy 17p syndrome involves duplication of 17p11→pter, and has been reported in 6 patients [Martsolf et al., 1988]. The trisomy 17q syndrome most commonly involves duplication of 17q23–qter [Lenzini et al., 1988], although several reports include bands 17q21–qter [Gallien et al., 1981; Serotkin et al., 1988; King et al., 1991]. Our patient's mosaic karyotype shows an apparent duplication of the segment 17p13q21.3, which is comparable to the cases of Yamamoto et al. [1979] and Palutke et al. [1976]. The phenotypes of these 3 patients show some common traits (Table I).

Mosaicism for a supernumerary marker chromosome originating from chromosome 17 euchromatin was associated with minor anomalies and severe intellectual handicap in this patient. The pattern of anomalies is unique and could be characteristic of this duplicated chromosome, although comparison with further cytogenetically proven cases will be required before the natural history can be predicted confidently from clinical and cytogenetic manifestations. No neurophysiological studies have been performed, although the patient is trisomic for 17p11.2, the chromosomal region duplicated in Charcot-Marie-Tooth syndrome type 1A; she therefore could have a peripheral neuropathy.

The clinical significance of supernumerary chromosomes poses a problem for the genetic counselor when they are diagnosed prenatally or in the young child. The phenotypic effect of a marker chromosome has been related to its size, to the amount of heterochromatic material present, to the chromosomal origin, and to the degree of mosaicism or tissue specificity of the marker. As many supernumerary ring chromosomes disappear in vivo, leaving only cells with a normal karyotype, they may often be undetected in carrier patients and are likely to be underreported in the cytogenetic literature.

This case report illustrates how accurate identification of supernumerary chromosomes can permit the description of new chromosomal syndromes and the delineation of their prognosis and natural history.

TABLE I. Clinical Findings in dup(17)(p13q21)

	Palutke et al. [1976]	Yamamoto et al. [1979]	Our patient
Sex	F	F	F
Age (years)	11	3	5
Duplication	17 pter–q21	17 pter–q21	most17?p13q21
Mental retardation	Severe	Severe	Severe
Microcephaly	+	–	–
Microstomia	+	+	–
Micrognathia	+	–	–
Ptosis	+	–	–
Coloboma	–	+	+
Abnormal ears	+	–	+
Polydactyly	+	+	+
Contractures	+	+	+
Hearing loss	+	?	+
Seizures	+	–	–

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